#39
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DOCKET NO.: ISIS-3105 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Teng et al.

Serial No.: **09/108,673** Group Art Unit: **1636**

Filed: **July 1, 1998** Examiner: **W. Sandals**

For: **COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL**

I, **Michael P. Straher**, Registration No. **38,325** certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On October 9, 2002

Michael P. Straher, Reg. No. 38,325

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Mark K. Wedel, M.D., J.D., do hereby declare as follows:

1. I am currently Executive Director of Clinical Development at Isis Pharmaceuticals, Inc. ("Isis") in Carlsbad, California, where I am responsible for designing, implementing, supervising and evaluating clinical trials for oligonucleotide drug candidates. I have both an M.D. and J.D. degree and am Board certified in Internal Medicine, Pulmonary Medicine, Sleep Disorders Medicine and Critical Care Medicine. I have been involved in clinical trials for about six years. My *curriculum vitae* is attached hereto as Exhibit A.

2. From 1987-2001, I was an Attending Intensivist, Scripps Clinic & Research foundation ICU, where I was responsible for the care and treatment of critically ill patients in intensive care, including post operative heart patients, liver transplants, respiratory, cardiac, renal and hepatic failure.

3. From 1995 to 2001, I was Director of Medical Affairs, Alliance Pharmaceutical Corp., San Diego, California, where I was responsible for evaluating and awarding external preclinical research, author of Phase 2 and Phase 3 protocols, and developed and coordinated clinical development plans, regulatory strategies, FDA interactions, clinical trial conduct, ICU clinical site selection and management, CRO selection, budget development and negotiations.

4. From 1987-1995, I was Medical Director of the Medical/Surgical Intensive Care Unit, Green Hospital of the Scripps Clinic & Research foundation, La Jolla, California.

5. From 1976-1987, I was Head, Division of Pulmonary Medicine, Park-Nicollet medical Center, Minneapolis, Minnesota, and Director of Respiratory Care Services, Methodist Hospital, Minneapolis, MN.

6. A phase I/II dose ranging human clinical trial of an ICAM-1 antisense oligonucleotide, ISIS 2302, in an enema formulation for ulcerative colitis ("UC") was conducted. The entry criteria for the study were that the individuals had to be at least 18 years of age; had active ulcerative colitis extending 5-50 cm from the anal verge; had a disease activity index ("DAI") score of 3-10, including an abnormal endoscopy score; were not currently taking medications or were on stable background oral 5-acetylsalicylic acid (the most common UC treatment) for greater than two months; had a negative stool culture; and had no history of bowel resection or stricture. The DAI categories are shown in Exhibit B which is attached hereto.

7. Forty patients were enrolled in the dose escalation by cohort study, ten subjects (8 active/2 placebo) per dose cohort. Four doses plus placebo were used: 0, 0.1, 0.5, 2 or 4 mg/ml of ISIS 2302 in a total enema volume of 75 ml which delivered 60 ml of fluid. The patients were dosed nightly for 4 weeks, enema retention time was recorded and patient progress was followed for 5 months.

8. The evaluation involved DAI at baseline and months 1, 3 and 6; monthly determination of clinical activity index ("CAI"); monthly erythrocyte sedimentation rate; and pre- and post-dosing colon biopsies for ICAM-1, histology and pharmacokinetics. The CAI criteria are shown in Exhibit C which is attached hereto. The DAI and CAI changes from baseline were compared to placebo. The median DAI scores are shown in Exhibit D which is attached hereto. These results show a significant decrease in median DAI scores, indicating significant therapeutic results, in individuals treated with the ISIS 2302 enema formulation compared to patients who received the placebo. Similarly, the median decrease in CAI is shown in Exhibit E, attached hereto. This shows that ISIS 2302 also significantly decreased the CAI, which also translates into a much improved clinical picture.

9. The time to new UC medication (5-ASA treatment; remedication) is shown in Exhibit F, attached hereto. This graph shows that in patients administered the highest dose of ISIS 2302 (4 mg/ml), none required standard 5-ASA treatment (remedication) after six months of

enema treatment, and in patients administered 2 mg/ml of ISIS 2302, remedication was not required in the majority of patients for more than four months. In contrast, patients administered the placebo or the lowest dose of ISIS 2302 required remedication after much shorter periods of time.

10. Thus, ISIS 2302, when presented in an enema formulation, significantly improved both the DAI and CAI endpoints after one month of 4 mg/ml dose compared to placebo. These improvements persisted and reduced the need for additional therapies during the six month follow-up period.

11. I declare that all statements made herein are of my own knowledge true and statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Mark K. Wedel, M.D., J.D.

1 OCT '02
Date

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EXHIBIT A

CURRICULUM VITAE

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909-693-4004

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BIRTHDATE: May 4, 1946
BIRTHPLACE: Eston, Saskatchewan, Canada
CITIZENSHIP: USA .

EDUCATION:

(1) JD, cum laude, May 1994, Western State University School of Law, San Diego, California. Law Review member, spring 1992; Law Review author, fall, 1993

(2) MD, summa cum laude, Phi Beta Kappa, class rank 2/97, The Johns Hopkins School of Medicine, Baltimore, Maryland, 1972

(3) BA, summa cum laude, Valparaiso University, Valparaiso, Indiana, 1968

POSTGRADUATE TRAINING:

Internship:	1972-73	University of California, San Diego (Internal Medicine)
Residency:	1973-74	University of California, San Diego (Internal Medicine)
Fellowship:	1974-76	University of California, San Diego (Pulmonary Medicine)

SPECIALTY BOARD CERTIFICATIONS:

Board certified in Internal Medicine	1975
Board certified in Pulmonary Medicine	1976
Board certified in Sleep Disorders Medicine	1984
Board certified in Critical Care Medicine	1987

POST TRAINING POSITIONS HELD:

(1) <u>2001 to present</u>:

- Executive Director, Clinical Development, Isis Pharmaceuticals

  Responsible for the development and coordination of the following compounds in development:
  - topical antisense oligo for ulcerative colitis
  - topical antisense oligo ICAM-1 inhibitor for psoriasis
  - intravitreal antisense oligo C-Raf kinase inhibitor for neovascularization
  - systemically administered antisense oligo for Hepatitis C

(1) <u>1995 to 2001</u>:

- Director of Medical Affairs, Alliance Pharmaceutical Corp.
- Director, Pulmonary Therapeutics, Alliance Pharmaceutical Corp.

  Responsible for the following:
  - Representing the critical care community to Alliance
  - Representing Alliance to critical care community
  - Evaluating and awarding external preclinical research
  - Presentation of LiquiVent program to outside investors
  - Presentation of LiquiVent program to potential licensing partners

- Author of LiquiVent clinical development program
    - author of current Phase 2 and Phase 3 protocols
- Appearances before FDA and HPB regulatory bodies
- Extensive teaching and lecturing responsibilities
- Extensive media appearances on behalf of Alliance, including PBS, CBS Good Morning Show, Discovery Channel, Scientific American, Public Broadcasting
- Director, Liquid Ventilation project, responsible for - development and coordination of clinical development plan, regulatory strategy, FDA interactions, clinical trial conduct, ICU clinical site selection and management, CRO selection, budget development & negotiations
- responsible for development of overall corporate plan for pulmonary therapeutics, including choice of drug candidates, formulations, selection and design of clinical trials

- Consultant, US Department of Justice, Southern California Division
-Health Care fraud prosecution unit

(2) 1987 to 2001:

- Attending Intensivist, Scripps Clinic & Research Foundation ICU, responsible for care and treatment of critical ill patients in Intensive Care, including post operative heart patients, liver transplants, respiratory, cardiac, renal and hepatic failure

(3) 1987-1995:

- Medical Director of the Medical/Surgical Intensive Care Unit, Green Hospital of the Scripps Clinic & Research Foundation, La Jolla, California

(4) 1976-1987:

- Member, Department of Internal Medicine, Park-Nicollet Medical Center, Minneapolis, Minnesota
- Head, Division of Pulmonary Medicine, Park-Nicollet Medical Center, Minneapolis, Minnesota
- Director, Respiratory Care Services, Methodist Hospital, Minneapolis, Minnesota
- Director, Sleep Disorders Laboratory, Methodist Hospital, Minneapolis, Minnesota

PROFESSIONAL SOCIETIES:

Phi Beta Kappa	The Johns Hopkins University School of Medicine
Alpha Omega Alpha	The Johns Hopkins School of Medicine

Member	American College of Physicians
Member	American College of Chest Physicians
Member	Society of Critical Care Medicine
Member	American Thoracic Society
Member	California Thoracic Society
Member	California Medical Association
Member	American Medical Association
Member	Association of Sleep Disorders Centers
Member	WSU Alumni

CURRENT PROFESSIONAL RESPONSIBILITIES:

Director of Medical Affairs, Alliance Pharmaceutical
Program Director, Pulmonary Therapeutics, Alliance Pharmaceutical
Attending Intensivist, Scripps Clinic & Research Foundation
Member, Scripps Clinic Medical Group, La Jolla

REFERENCES and/or BIBLIOGRAPHY:

Available upon request

EXHIBIT B

DAI (max score = 12)

- Stool Frequency (0-3)
  - 0 healthy (typical frequency during remission)
  - 1 1-2/day
  - 2 3-4/day
  - 3 >4/day
- Rectal Bleeding (0-3)
  - 0 none
  - 1 streaks with <50% of stools
  - 2 obvious blood with most of stools
  - 3 blood alone passed
- Endoscopic Score (0-3)
  - 0 normal/inactive
  - 1 mild: erythema, friability, decreased vasculature
  - 2 moderate: " " , or erosions
  - 3 severe: spontaneous bleeding or ulcerations
- Investigator's Global (0-3)
  - healthy/remission; mild, moderate or severe UC

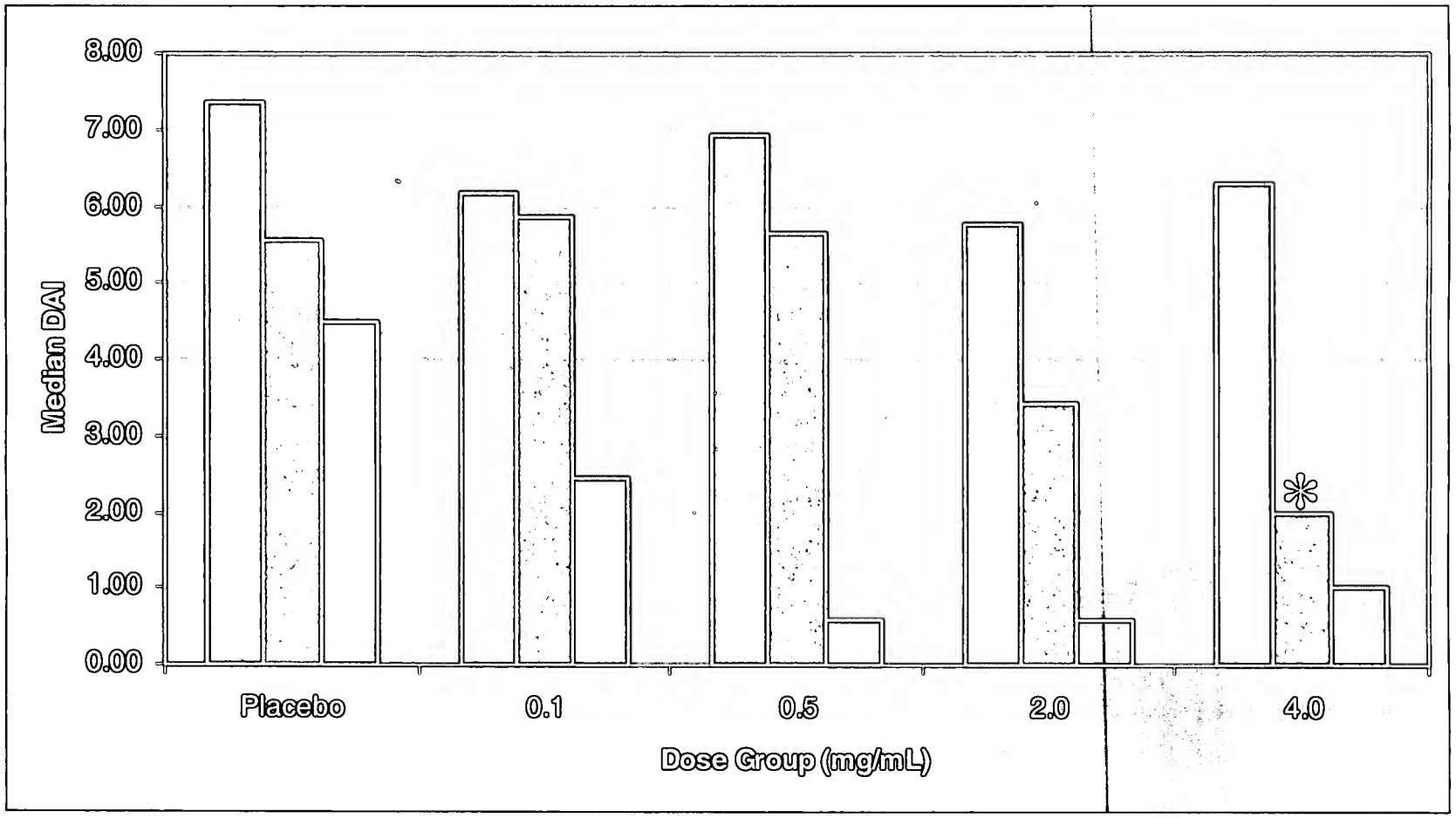
EXHIBIT C

CAI (max score = 21)

- Stool Frequency (0-4)
- Nocturnal Diarrhea (0-1)
- Visible blood in stool (0-3)
- Fecal incontinence (0-1)
- Abdominal pain or cramping (0-3)
- General Well-being (0-5)
- Abdominal Tenderness (0-3)
- Need for anti-diarrheal drugs (0-1)

EXHIBIT D

2302-CS12 Median DAI Scores (0, Mo 1, Mo 3) by ISIS 2302 Enema Concentration

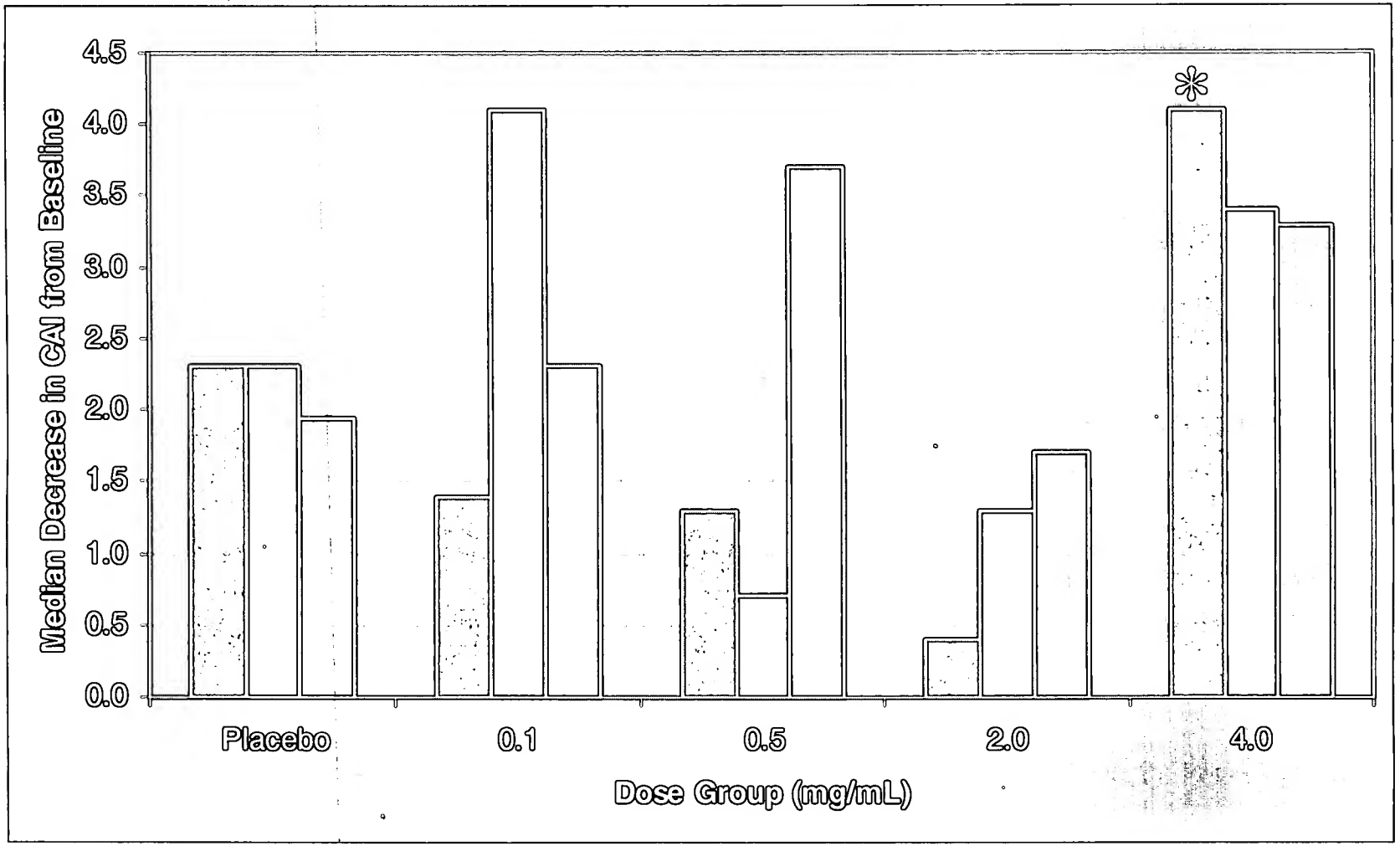


* p = 0.034 for change from baseline vs. placebo
4 mg/mL enema cohort:
2/8 with DAI = 0 at Month 1
1/8 with DAI = 0 at Months 3/6
N = 8 except where noted

ISIS PHARMACEUTICALS

EXHIBIT C

2302-CS12 Median Decrease in CAI (Months 1, 2, 3) by Enema Concentration

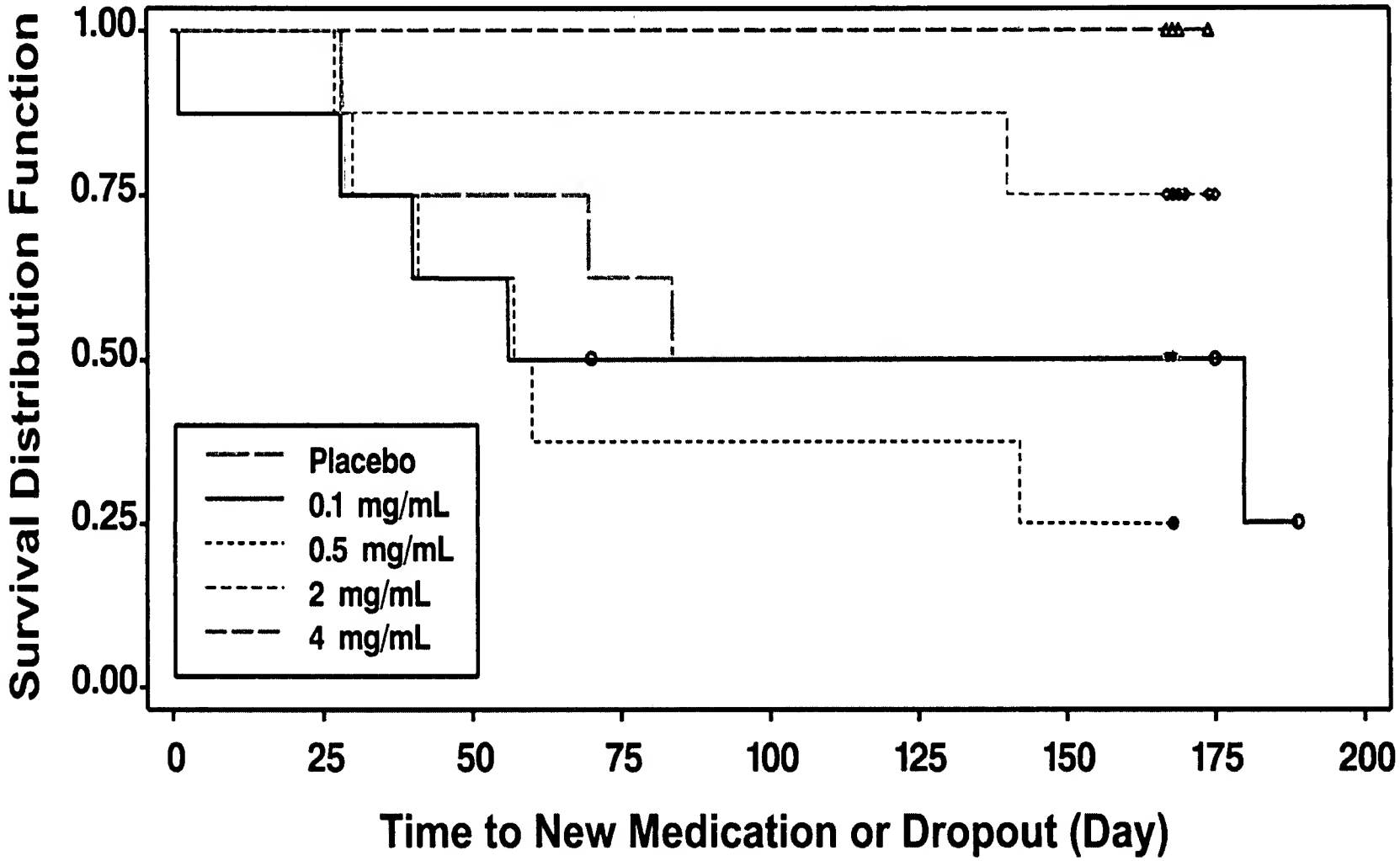


* p = 0.39 [Decrease from baseline vs. placebo]
N = 8 except where noted

ISIS PHARMACEUTICALS

EXHIBIT F

2302-CS12
Time to New UC Medication Use or Dropout



ISIS PHARMACEUTICALS